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With international search report.

(54) Title: USE OF TAUROLIDINE AND/OR TAURULTAM FOR THE TREATMENT OF TUMOURS

(57) Abstract

The present invention relates to a method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.

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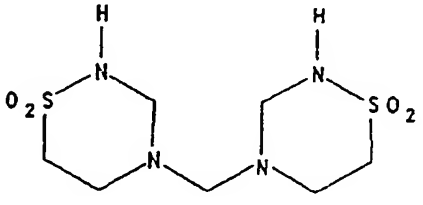
USE OF TAUROLIDINE AND/OR TAURULTAM FOR THE TREATMENT OF TUMOURS

This invention relates to the treatment of tumours by chemotherapy.

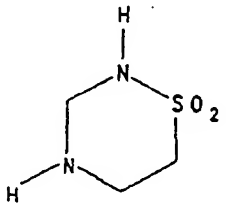
The antibacterial and anti-toxin drug taurolidine and the related product taurultam have recently been shown to exert a modifying effect on the toxicity of tumour necrosis factor (TNF) which is used, inter alia, in the treatment of tumours. Our United Kingdom Patent Application No 9005856.1 relates to combined therapy using TNF and taurolidine or taurultam. In the course of these studies, it was surprisingly found that taurolidine acted directly on tumours in addition to its effect on TNF. Furthermore, such action was shown to be selective in that the growth of normal cell-lines was not significantly inhibited.

According to the present invention we provide a method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.

Taurolidine and taurultam have the formulae given below:



TAUROLIDINE



TAURULTAM

These compounds are methylol transfer agents. Taurolidine acts by transferring three methylol groups at the site of action, taurultam being an intermediate metabolite which itself transfers a single methylol group with liberation of the very well tolerated compound taurinamide. Thus, the two compounds act by essentially the same mechanism. It should be noted that methylol transfer is to be contrasted with methyl transfer which is characteristic of many highly toxic anti-tumour drugs. Taurolidine and taurultam have low toxicity and are not cytotoxic against normal cells.

The taurolidine or taurultam may be administered systemically, ie. by injection or infusion, or by direct application, eg topically, to external tumours.

Suitable formulations for injection or infusion may comprise an isotonic solution containing one or more solubilising agents, eg polyols such as glucose, in order to provide solutions of increased taurolidine or taurultam concentration. Such solutions are described in our European Patent Application 253662. The concentration of taurolidine or taurultam in such solutions may be in the range 1 to 10 g/litre.

Taurolidine and/or taurultam may be administered in the dose range 150 to 450 mg/kg per day, preferably 300 to 450 mg/kg per day. Relatively large volumes of aqueous solutions containing taurolidine or taurultam will thus often require to be administered, containing for example 10g to 30g of taurolidine and/or taurultam. It may be convenient to administer these compounds by infusion in view of the relatively large volumes concerned, conveniently at intervals throughout the day.

It is believed that other agents known to be involved in tumour metabolism may also advantageously be co-administered in conjunction with the above combined therapy. Such agents include gamma-interferon, interleukin-1 and interleukin-2. Cytotoxic agents such as adriamycin and actinomycin D may also be co-administered.

The tumours to be treated may be of any type, including lymphomas, sarcomas, melanomas and carcinomas. It is particularly beneficial to use taurolidine and/or taurultam prevent the spread of metastases, especially following surgical removal of tumours. The mammalian subjects are typically humans.

The invention also includes the use of taurolidine and/or taurultam for the treatment or prophylaxis of tumours in mammalian subjects.

The invention further includes the use of taurolidine and/or taurultam for the preparation of pharmaceutical compositions for the treatment or prophylaxis of tumours in mammalian subjects.

The following examples are given by way of illustration only:-

Example 1

C573L/6 mice injected iv with 1.5×10^6 B16 melanoma cells were treated with a) ip normal saline tid on days 0-10, b) ip taurolidine 4.0mg tid on days 0-10, and c) ip taurolidine 4.0mg tid on days 3-10. Mice were sacrificed on day 10 and pulmonary metastases counted. When taurolidine treatments started on the day of tumour injection, the number of pulmonary metastases was

significantly reduced compared either to the control group or to Group C ($p<0.05$).

Treatment Group	n	Mean Pulmonary Metastases ± S.E.M
Saline	25	117.3 ± 18.5
Taurolidine (D 0-10)	16	76.4 ± 14.9
Taurolidine (D 3-10)	16	103.5 ± 14.8

In a second in vivo experiment, Balb/c mice injected sc with 1.5×10^6 Meth A sarcoma cells received either no treatment or taurolidine 2mg ip bid for seven days. At seven days 90% (27/30) of the control animals had palpable tumour growth, while only 40% (12/30) of the taurolidine treated mice had detectable tumour growth (p-0.0.02). In a third series Balb C mice received IP injections of meth A followed by either a) saline 0.1 ml IP BD or b) taurolidine 0.1 ml IP BD for 7 days. At 7 days 28/32 saline treated mice had ascites in comparison to 0/32 of taurolidine treated mice ($p<0.0001$). Actuarial survival of saline treated mice was also significantly impaired (p,0.005).

Example 2

Taurolidine was tested against multiple cell lines (two tumours, one normal) using a range of doses.

Cell line tested (%)	Concentration (μg ml)	Inhibition of cellular metabolism
Foreskin Fibroblasts	20	31.7
LS174T (colon)	20	84.3
Jurkat (leukaemic)	20	84.6

Preferential activity against tumour lines was demonstrated at low doses with complete cellular inhibition of tumour, but not normal cells, occurring at doses > 200 μg ml

CLAIMS

1. A method of treatment or prophylaxis of tumours in mammalian subjects wherein an effective dose of taurolidine and/or taurultam is administered to a mammalian subject suffering from or at risk to tumour growth.

2. A method as claimed in Claim 1 wherein said taurolidine and/or taurultam is administered by injection or infusion or by direct application to external tumours.

3. A method as claimed in Claim 1 or Claim 2 wherein said taurolidine and/or taurultam is administered at a dosage in the range of 150-450 mg/kg per day.

4. A method as claimed in Claim 3 wherein said taurolidine and/or taurultam is administered at a dosage in the range of 300 to 450 mg/kg per day.

5. A method as claimed in any one of Claims 1 to 4 for the treatment or prophylaxis of lymphomas, sarcomas, melanomas and carcinomas.

6. A method as claimed in any one of Claims 1 to 5 further comprising administering to said mammalian subject separately or simultaneously cytotoxic agents or agents known to be involved in tumour metabolism.

7. A method as claimed in Claim 6 comprising further administering gamma-interferon, interleukin-1, interleukin-2, adriamycin or actinomycin D.

8. Use of taurolidine and/or taurultam for the treatment or prophylaxis of tumours in mammalian subjects.

9. Use of taurolidine and/or taurultam for the preparation of pharmaceutical compositions for the treatment or prophylaxis of tumours in mammalian subjects.

10. A pharmaceutical composition comprising taurolidine and/or taurultum and at least one agent selected from cytotoxic agents or agents involved in tumour metabolism for separate or simultaneous administration to a mammalian subject suffering from or at risk to tumour growth.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01269

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/54

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
P,X	Annals of the Royal College of Surgeons of England, vol. 72, 1990, M.E. Lucarotti et al.:"Antiseptic Toxicity to Breast Carcinoma in Tissue Culture: An Adjuvant to Conservation Therapy?", pages 388-392, see the whole document	9
A	EP,A,0139534 (Ed. GEISTLICH AG) 2 May 1985, see abstract; claims	9,10
A	J.E.F. Reynolds: "Martindale", The Extra Pharmacopoeia, 29th Edition, 1989, The Pharmaceutical Press, (London, GB), page 162, "Taurolidine", see the whole article	9,10

-/-

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30-09-1991	14. 10. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PEIS M. Peis

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	Annals of Royal College of Surgeons of England, vol. 66, No. 3, May 1984, Henry C. Umpleby et al.:"The Efficacy of Agents Employed to Prevent Anastomotic Recurrence in Colorectal Carcinoma", pages 192-194, see the whole document	9

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 1 -8 because they relate to subject matter not required to be searched by this Authority, namely:

Pls. see Rule 39.1(iv) - PCT
Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic mehtods.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9101269
SA 48878

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 08/10/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0139534	02-05-85	AU-A- 3457484	09-05-85
		BE-A- 900855	15-02-85
		CH-A- 660969	30-06-87
		DE-A- 3438470	30-05-85
		JP-A- 60105617	11-06-85
		US-A- 4604391	05-08-86